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# Scientific Update™

## New Evidence in the Management of Cardiovascular Risk: The Place of Heart Rate

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**Although heart rate (HR) is an easily-obtained clinical variable, its value in assessing prognosis is not widely known. Resting HR and changes in HR during exercise and recovery from exercise are mediated by the balance between sympathetic and vagal activity. The importance of HR in determining myocardial oxygen demand is well-recognized, but the pathophysiological role of HR in cardiovascular disease (CVD) remains controversial. There is extensive epidemiologic data demonstrating the prognostic implications of a high resting HR in the general population and in patients with documented CVD. The benefit of HR reduction in patients presenting with a wide range of CV diagnoses has been demonstrated; however, the specific role of HR reduction as a therapeutic goal is less well-accepted or understood. This issue of *Cardiology Scientific Update* explores these aspects of resting HR and challenges physicians to seriously consider this variable in the future management of patients with CVD.**

### Pathophysiological role of heart rate

As HR increases, myocardial oxygen demand ($MVO_2$) increases, and there is a concurrent increase in coronary blood flow (CBF) mediated by metabolic coronary vasodilation. The minute $MVO_2$ for a constant minute of cardiac work increases monotonically with increases in HR from 100 to 200 beats/min (bpm), being at a minimum at the lowest HR.[1] This relationship can be ascribed to the HR-proportionate increase in the $MVO_2$ required for excitation-contraction coupling. However, as CBF occurs predominately during diastole, the increase in HR reduces the fraction of the cardiac cycle occupied by diastole and may compromise CBF. A reduction in HR would, therefore, allow a relative increase in CBF.

In patients with stable angina, there is a pressure gradient across a significant coronary stenosis. With an increase in HR, peripheral resistance in the coronary tree is reduced. While there is an increase in CBF to myocardium supplied by a normal artery, there is a significant fall in CBF to myocardium supplied by a stenotic artery.[2] Thus, there is redistribution of bloodflow away from post-stenotic myocardium as HR increases. However, collateral circulation is less effective in maintaining blood flow in the post-stenotic myocardium as HR increases[3] and the reduction in infarct size with beta-blockade is eliminated if an increased HR is maintained.[4] Reducing HR during exercise and during acute myocardial infarction (MI) decreases ischemia, leading to improvement in left ventricular function and decreased infarct size, respectively.

A reduction in HR by ivabradine, a new therapeutic entity whose singular effect is to reduce HR, does not adversely affect the normal increase in mean CBF velocity and decrease in coronary vascular resistance that occurs during exercise; whereas beta-blockade attenuates velocity and increases resistance. Ivabradine does not affect resting epicardial coronary artery diameter and only attenuates its increase during exercise, whereas propranolol reduces it at rest and maintains a significant constriction of these large vessels throughout the exercise period. A direct reduction in HR is likely to be beneficial at rest or during exercise in patients with ischemic heart disease.[5]

There is a strong relationship between HR and the development and progression of atherosclerosis. Low HR variability predicts a rapid progression of coronary artery



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disease and has been a valuable traditional risk marker of atherosclerosis.[6] Hemodynamic forces are associated with the future development of plaque disruption. Left ventricular muscle mass and elevated HR are significantly associated with an increased incidence of plaque disruption.[7] Patients on ß-adrenergic blocker therapy have a reduced incidence of disruption of vulnerable plaques.[7] Resting HR is an index of dominant sympathetic nervous activity, which may increase coronary vasoconstriction, enhance myocardial oxygen consumption, reduce diastolic perfusion time, increase endothelial shear stress and platelet aggregation, release growth factors, and increase plaque instability.

## Prognostic value of heart rate in healthy populations

A review by Palatini[8] clearly demonstrates that an elevated HR is associated with a greater risk of developing hypertension and atherosclerosis and that it is a potent predictor of CV morbidity and mortality. These relationships have been shown in general populations. The risk related to a rapid HR remains highly significant after controlling for major risk factors for atherosclerosis, suggesting that it plays a direct role in the induction of risk. Risk factors for coronary artery disease cluster in subjects with a high HR, suggesting that sympathetic overactivity may account for the increased CV morbidity in subjects with tachycardia. The hemodynamic disturbances related to a rapid HR have a direct impact on the arterial wall and promote the development of atherosclerotic plaques. Drug-induced reductions in HR in patients with MI or congestive heart failure may be beneficial in several clinical conditions.

In 5,713 asymptomatic working men, Jouven et al (Figure 1)[9] demonstrated that the risk of sudden death from MI was increased in subjects with:

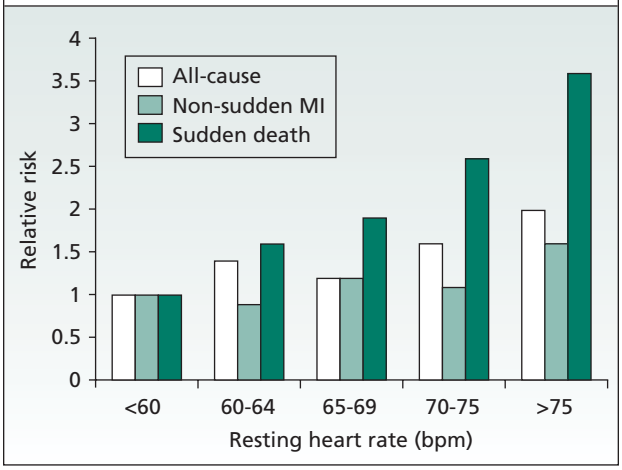
- a resting HR of >75 bpm; relative risk (RR) = 3.92
- an increase in HR during exercise that was < 89 bpm; RR = 6.18
- a decrease in HR of <25 bpm after the termination of exercise; RR = 2.20.

Additional predictors of risk include elevated body mass index (BMI), tobacco use, and lack of exercise. HR remains significant after adjustment for confounding variables. Interestingly, HR predicted sudden death, but not nonsudden death. These data suggest that physicians should be attentive to patients with a resting HR of >75 bpm, an attenuated HR response to exercise, and slow recovery of HR with exercise, since these factors predict sudden death. The most physiologic intervention to improve these measures is exercise training.

## Prognostic value of heart rate in patients with CV diseases

The relationship between HR and clinical outcomes has been demonstrated, not only in the general population, but also among hypertensive individuals. This has important implications for the treatment of hypertension, in that patients with higher HRs at rest may be best suited to HR-lowering antihypertensive agents. In a total of 2293 men and women taking placebo, with baseline systolic blood pressures (SBPs) of 160 to 219 mm Hg and diastolic (DBPs) of <95 mm Hg, a raised baseline clinic HR was positively associated with a worse prognosis for total, CV, and non-CV mortality.[10] Patients with HRs that were >79 bpm (top quintile) had a 1.89 times greater risk of mortality than subjects whose HR was ≤79 bpm (95% confidence interval (CI), 1.33-2.68). Predictors of death were heart rate ($P<.001$), age ($P<.001$), serum creatinine level ($P=.001$), presence of diabetes ($P=.002$), previous CV disease ($P=.01$), triglyceride level ($P=.02$), smoking ($P=.04$), and elevated BP ($P=.05$). The relationship between HR and mortality was quantitatively similar in both men and women.

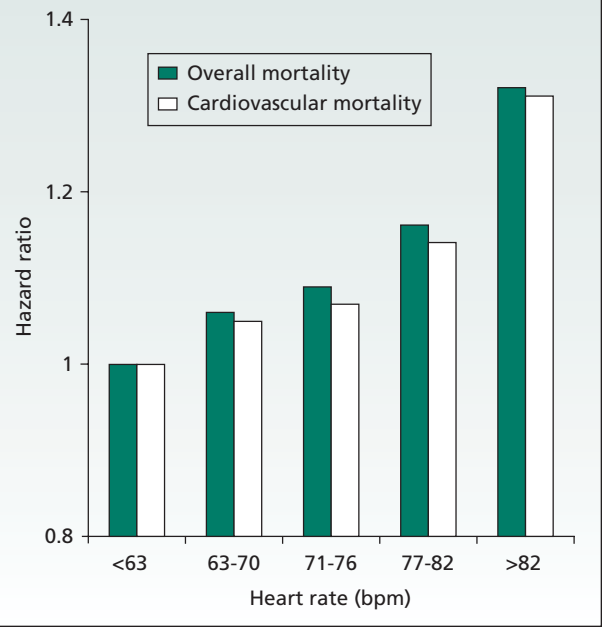
**Figure 1: Relationship between the risk of sudden death and resting HR[9]**




In the Coronary Artery Surgery Study registry, a total of 24,913 patients with suspected or proven coronary artery disease (CAD) were studied for a median follow-up of 14.7 years.[11] Increasing resting HR predicted all-cause and CV mortality and CV rehospitalizations ($P<0.0001$). Compared to the reference group, patients whose resting HR was ≥83 bpm at baseline (Figure 2) had a significantly higher risk for total mortality (hazard ratio=1.32; CI, 1.19–1.47, $P<0.0001$) and CV mortality (hazard ratio=1.31; CI, 1.15–1.48, $P<0.0001$). HR was a predictor of rehospitalization, CV events, and congestive heart failure, and was independent of clinical variables, including age, gender, ejection fraction, diuretics, and other risk factors in patients with CAD.

Heart rate after an acute MI is an index of late mortality. HR is included in the *Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico* (GISSI) risk chart for predicting the absolute risk of death post-MI.[12] In patients with heart failure, the Carvedilol Or Metoprolol European Trial

**Figure 2: Relationship between increasing resting HR and risk for overall mortality and CV mortality[11]**



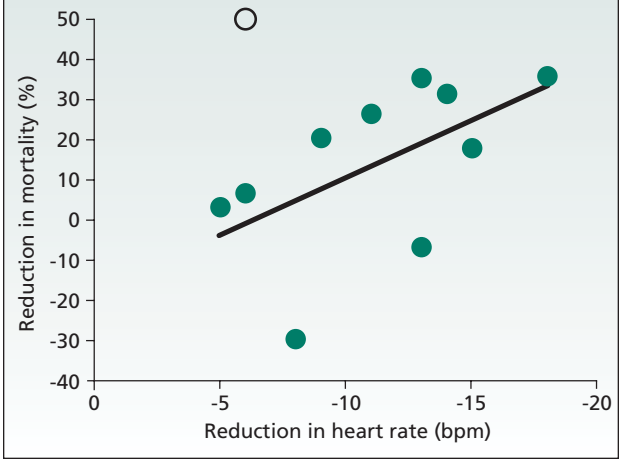

(COMET) trial demonstrated that beta-blocker dose and the HR, and SBP achieved during beta-blocker therapy were independent predictors of outcome. Specifically, a resting HR >68 bpm was an independent predictor of mortality.[13]

An increase in HR also provokes myocardial ischemia in patients with stable angina by increasing myocardial demand. The majority of ischemic episodes observed during Holter monitoring of ST segments are preceded by an increase in HR of ≥10 bpm, with a more dramatic increase in the 5 minutes before ST depression.[14] An ischemic episode occurs 80% of the time when the HR reaches the exercise ischemic threshold. The number of episodes was related to the frequency that HR increased above the ischemic threshold. Therefore, reducing HR with medical therapy during daily activities would reduce the number of ischemic episodes. A similar relationship between HR and ischemic episodes in unstable angina has been demonstrated.[15]

## HR lowering and benefits on CV death: the level of evidence

In the treatment of acute MI in the 1970s, it was observed that lowering the HR reduced chest pain, ST elevation, arrhythmias, myocardial damage, and left ventricular dysfunction. The efficacy of metoprolol, timolol, and propranolol was greatest in patients whose HR was greater than the median.[16,17] A reduction in HR of at least 15 bpm during infarct evolution was associated with a reduction in infarct size of between 25% and 30%. A reduction in HR of <8 bpm has no effect or may actually increase infarct size. Figure 3

**Figure 3: Relationship between a reduction in resting HR and the reduction in mortality[18]**

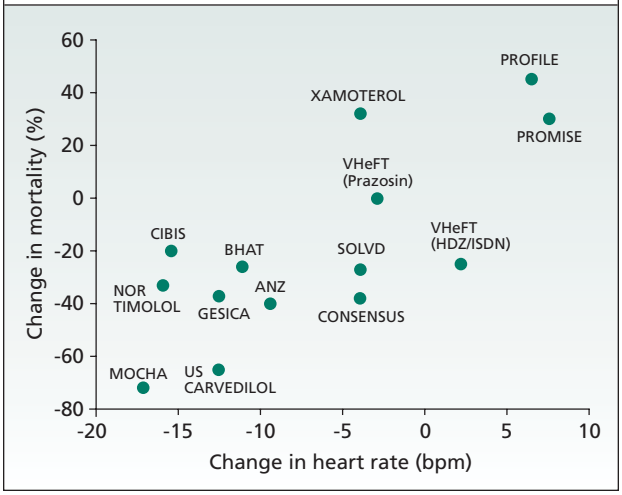



O = The open circle indicates a small study excluded from the regression equation.

shows the relationship between the actual reduction in resting HR and the percentage of reduction in mortality. The beneficial effect of beta-blockers is related to a quantitative reduction in HR. An HR of >70 bpm was associated with a 2.5-fold increase in mortality as compared to an HR <70 bpm. There is a reduction in ventricular fibrillation, sudden death, and mortality with beta-blocker therapy in patients with a higher HR.

In congestive heart failure therapy, a reduction in HR with therapy improves outcome.[18] HR reduction was the most powerful predictor of outcome in the Cardiac Insufficiency Bisoprolol Study (CIBIS) trial.[19] There is a strong relationship between change in HR and outcome in congestive heart failure as shown in Figure 4. All of these studies demonstrate

**Figure 4: Relationship between HR and mortality in HF trials[24]**



that HR reduction in angina, MI, and congestive heart failure is an important therapeutic target that results in a significant reduction in morbidity and mortality.

## Slowing heart rate – a therapeutic goal in CV disease?

The preceding discussion demonstrates the importance of HR reduction in acute MI and congestive heart failure. In 1632, Hyde suggested that a reduction in HR would be of benefit in patients with exertional chest pain. Even if HR is a prognostic factor, rather than a risk factor, the therapeutic approach to HR reduction is well-accepted and documented. In the treatment of angina pectoris, Stone et al demonstrated that HR reduction with beta-blockers is important as an effective strategy for prevention of ischemia and improvement in exercise tolerance,[20] since an increase in HR precedes ST depression, left ventricular dysfunction, and chest pain.[21]

The reduction in HR can be achieved with beta-blockers, and nondyhydropyridine calcium antagonists. Ivabradine (not yet available in Canada) inhibits the pacemaker activity of the sinoatrial node and produces a dose-dependent improvement in exercise tolerance and time to development of ischemia during exercise.[22,23] If a reduction in cardiac events is observed in further studies with ivabradine, it is possible that the hypothesis that HR is an independent factor for CV events could be proven.

## Conclusions

Heart rate is an important determinant of outcome in patients with known or suspected CV disease. Treating patients with acute MI, congestive heart failure, or demonstrable stress-induced ischemia using medications that reduce HR improves symptoms and reduces mortality and morbidity.

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